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Psychological research documents that the psychosocial burdens following breast cancer are notable in number, severity, and scope. A biobehavioral model of cancer stress and disease course has been proposed (see Andersen, Kiecolt-Glaser, & Glaser, 1994) and provides a conceptual basis for the proposed research. We will test the model with a clinical trial: 200 women with stage II or III breast cancer who have been recently diagnosed and surgically treated will be randomized between two conditions: (1) assessment and intervention, or (2) assessment only (control). In addition to documenting the quality of life benefits of a psychological intervention, this study provides an experimental test of the psychological and behavioral variables which may influence clinical outcomes directly. Further, we tested a specific mechanism--alteration in immune function--to achieve beneficial health effects for women with breast cancer.

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Barbara A. Anderson 9/11/95

PI - Signature Date

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INTRODUCTION

Background of Previous Work

We have proposed a biobehavioral model of cancer stress and disease course (see Andersen, Kiecolt-Glaser, & Glaser, 1994, for a full discussion). The model identifies the psychological and behavioral factors and the biologic mechanisms by which health outcomes and cancer progression might be influenced. This model provides the conceptual basis for the proposed research (see **Fig. 1**). Below we discuss each construct and pathway in the model.

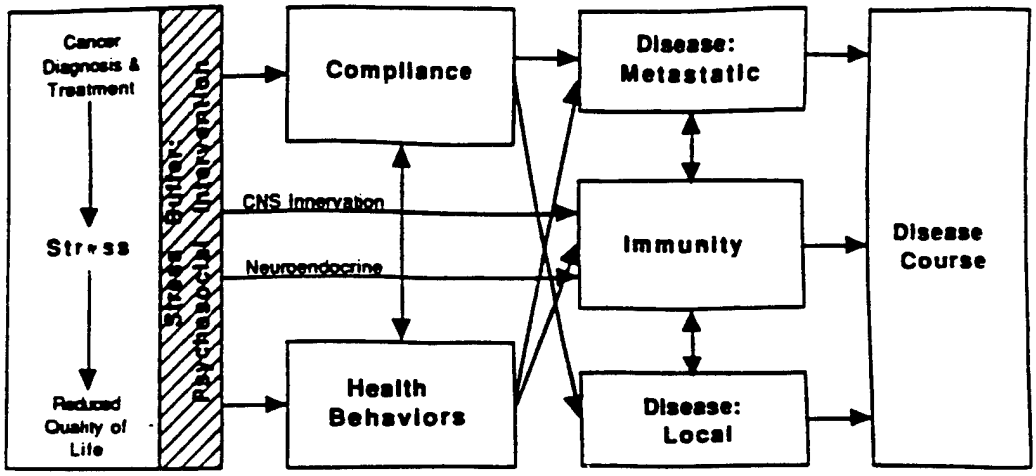

Figure 1: A biobehavioral model of the psychological (Stress and QoL), behavioral (compliance and health behaviors), and biologic pathways from cancer stressors to disease course. (CNS = Central Nervous System).

The cancer stressor and psychological factors: Stress and lowered quality of life. A cancer diagnosis and cancer treatments are objective, negative events. Although negative events do not always produce stress and lowered quality of life, data from many studies, including ours from gynecologic cancer patients (Andersen, Anderson, & deProsse, 1989a), document severe, *acute stress* at diagnosis. However, it is also clear that lengthy cancer treatments and disruptions in major life areas occur, thereby producing *chronic stress*. Emotional distress, in combination with the other life disruptions, can results in a stable, lower quality of life (e.g. Cella & Tross, 1986). Other permanent sequelae from breast cancer treatments, such as sexual problems and/or sterility, impact intimate relationships and social support (Schover, 1994). Unemployment, underemployment, job discrimination, and difficulty in obtaining health insurance can be problems for a substantial minority (Wingard, Curbow, Baker, & Piantadosi, 1991). Thus, many stressors occur for survivors (Andersen, 1994).

Behavioral factors: Health behaviors and compliance. The biobehavioral model suggests that there may be important health behavior sequelae (see arrow from cancer stress and lowered QoL to health behaviors in Fig. 1), specifically an increase in negative behaviors and/or a decrease in positive ones. There are many manifestations of negative health behaviors. Individuals who are depressed and/or anxious are more likely to self-medicate with alcohol and other drugs, and, in addition, *alcohol abuse* can potentiate distress (Grunberg & Baum, 1985). Distressed individuals often have *appetite disturbances or dietary changes* which are manifested by eating less often or eating meals of lower nutritional value. While there appear to be individual differences in this phenomena (Greeno & Wing, 1994), women may be more vulnerable and

women who have undergone changes in their eating habits (e.g. restriction due to cancer treatments) may have heightened vulnerability. For example, in a survey of 800 cancer patients being cared for at home, 38% reported regular problems with a low of appetite which they reported as unrelated to other problems they were having, such as nausea or vomiting (Wellisch, Wolcott, Pasnau, Fawzy, & Landsverk, 1989). On the other hand, a tendency for breast cancer patients receiving adjuvant chemotherapy to *gain weight* has been found (Camoriano, Loprinizi, & Ingle, 1990). Distressed individuals may report *sleep disturbances,* such as early morning awakening, sleep onset insomnia, and middle night insomnia (Lacks & Morin, 1992). *Cigarette smoking and caffeine use,* which often increase during periods of stress, can intensify the physiologic effects of psychosocial stress, such as increasing catecholamine release (Lane & Williams, 1985; Dews, 1984). Conversely, individuals who are stressed may not begin or abandon previous positive health behaviors, such as regular *physical activity.* Data suggest a positive relationship between physical activity or fitness and psychological health (Dubbert, 1992). In the case of breast cancer patients, positive mood effects as well as increased functional capacity were found for women receiving chemotherapy while participating in a program of aerobic interval training (MacVicar, Winningham & Nichel, 1989).

The model suggests that health behaviors may, in turn, affect immunity (see arrow from health behaviors to immunity in Fig. 1). A covariation of immunity and objective measures of sleep , alcohol intake, smoking, and drug use has been found (Holt, 1987; Irwin, Smith, & Gillin, 1992; Kronfol, Hill, Kroll, Brower, & Greden, 1993). Also, problematic health behaviors interact to produce detrimental immune consequences. For example, substance abuse has direct effects, as well as indirect effects via alterations in nutrition (Jaffe, 1980). Poor nutrition is associated with a variety of immunological impairments (Chandra & Newberne, 1977). Conversely, accumulating evidence suggests that physical activity may have positive consequence for both the immune and endocrine systems, even among individuals with chronic diseases [e.g. La Perriere et al. (1990) data with HIV-infected men]. In summary, distressed individuals tend toward detrimental health behaviors that may potentiate their stress and, concurrently, negatively affect their immunologic functioning while positive health behaviors, such as exercise, may have the converse effect.

The model suggests that health behaviors may be directly related to disease progression (see arrow from health behaviors to disease: metastatic in Fig. 1). Considering all the health behaviors noted above, the strongest case can be made for the importance of nutrition and diet in breast cancer. A variety of data link nutrition/dietary factors and risk for breast cancer [e.g. epidemiologic data, animal models of high fat diet and tumor growth, obesity and the increase of breast cancer incidence (Howe et al., 1990; Simopoulos, 1987)]. More germane to the proposed research is data suggesting that increased fat intake, obesity at diagnosis, and weight gain may be related to recurrence and survival. The data regarding fat has been sufficiently strong to begin clinical trials of dietary interventions to reduce fat in breast cancer patients; recurrence/survival are the endpoints in these studies. Following two feasibility studies (Nutrition Adjuvant Study, NAS, Chlebowski, 1989; and the Women's Intervention Nutrition Study, WINS, Chlebowski, 1993), a second nationwide WINS study is now underway in which the fat reduction target is a rate of dietary fat of < 15% of energy. Alternatively, some suggest that fiber, rather than fat, is the critical dietary factor (Howe, Hiroahata, Hislow et al., 1990) in that fiber is postulated to modify serum estrogen levels by increased fecal excretion of estrogens. Finally, related data link weight gain after breast cancer to an increased risk of recurrence (e.g. Holm et al., 1993). Taken together these data suggest that behavioral factors relevant to nutrition, fat/fiber balance, and energy expenditure (vis-a-vis weight gain) may be relevant to disease progression.

The second behavioral factor noted in the model is *treatment (non)compliance* as the available data suggest that psychological factors may be important (see arrow from stress/QoL to compliance in Fig. 1). Compliance problems cross a wide range of diseases, therapies, and individual patient characteristics (e.g. Haynes, Taylor, & Sackett, 1979). In cancer, some patients become

discouraged and fail to complete treatment. A general implication of such behaviors is the invalidation of clinical trials, with an eventual adverse effect on overall patient survival (Haynes & Dantes, 1987). For the individual, dosage reductions can compromise his/her survival. A clear demonstration of this effect was data by Bonnadonna and Valagussa (1981) reflecting differential survival rates for women receiving $\geq$ 85%, 65-84%, or $\leq$ 65% of the recommended dosages of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) therapy for breast cancer. Surveying the literature we find that non compliance rates range from 8% (Taylor, Lichtman, & Wood, 1984) to 23-25% (Berger, Braverman, Sohn, & Morrow, 1988). Inclusion of "compliance" in the model presumes that a range of treatment regimen characteristics are considered, as the data suggest that different correlates exist for different compliance behaviors (Richardson, Marks, & Levine, 1988; Lebovits et al., 1990). The model suggest that poor compliance can effect local and/or metastatic control of the disease, and which route is affected depends on the treatment regimen as well as the characteristics of an individual's noncompliance.

The model also specifies that the processes governing compliance and health behaviors may interact (see double headed arrow between compliance and health behaviors in Fig 1) or even may be synergistic. That is, those who are compliant may expect better health outcomes and, thus, comply with diet, exercise, sleep, etc. or other behaviors indicative of "good health." The interaction of these behavioral phenomena may account, in part, for the positive main effect for compliance in randomized clinical trials of drug vs. placebo for coronary heart disease (Epstein, 1984; Coronary Drug Project Research Group, 1980). Despite their importance, health behavior and compliance variables have been understudied in psychological intervention studies, including those with immune outcomes (Kiecolt-Glaser & Glaser, 1992) and those without (Andersen, 1992). Further, changes in health behaviors and/or compliance have been offered as post hoc explanations some of the most notable intervention findings (e.g. survival difference in Spiegel, Bloom, Kraemer, & Gottheil, 1989).

Biological pathways. Stress sets into motion important biological effects involving the autonomic, endocrine, and immune system. Stress may be routed to the immune system by the central nervous system (CNS) via activation of the sympathetic nervous system or through neuroendocrine-immune pathways (see Fig. 1; de la Torre, 1994). In the latter case, a variety of hormones released under stress have been implicated in immune modulation (e.g. catecholamines, cortisol, prolactin, and growth hormone; see Baum, Grunberg, & Singer, 1982; Rabin, Cohen, Ganguli, Lysle, & Cunnick,1989; Sabharwal et al., 1992). Without considering any stress pathway (effect) to immunity, there is evidence for the importance of the immune responses in host resistance against cancer progression, and hence the arrows going in both directions from immunity to local and metastatic disease. Experts in the immunology/cancer area cite the following important findings with regards to the specific importance of NK cell activity: (1) patients with a variety of solid malignancies and large tumor burdens have diminished NK cell activity in the blood; (2) low NK cell activity in cancer patients is significantly associated with the development of distant metastases; and, (c) in patients treated for metastatic disease, the survival time without metastasis correlates with NK cell activity (see Whiteside & Herberman, 1989 for a review). These effects have also emerged for breast cancer patients. Specifically, NK cells have been shown to play an important role in the surveillance of tumor development and the occurrence of metastases (Hanna & Burton, 1986; White, Jones, Cooke, & Kirkham, 1982). Also, the level of NK activity has been correlated with prognostic factors, including tumor burden (Cunningham-Rundles, Fillipa, Braun, Antonelli, & Ashikari, 1981; Wiltschke et al., 1993) and estrogen receptor status (Zielinsky et al., 1989). Moreover, cancers etiologically linked to hormonal stimuli, as is the case for breast cancer, may be more responsive to stress effects (van der Pompe et al., 1994).

In preface, we note that both qualitative (Kiecolt-Glaser & Glaser, 1988; Cohen & Herbert, in press; Weiss, 1992) and quantitative (Herbert & Cohen, 1993 a & b) summaries of the PNI literature conclude that psychological distress and stressors (i.e. negative life events, both acute

and chronic) are reliably associated with immune down-regulation in non cancer populations. *Time limited (acute) stressors* can produce immunologic changes in relatively healthy individuals (Glaser et al., 1986, 1987, 1991). *Chronic stressors* are associated with down-regulation rather than adaption, with the largest NK cell effects found for lengthy stressors and/or ones which have interpersonal components (Herbert & Cohen, 1993b for review; Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991 for an example). Many of the qualities of chronic stressors [continued emotional distress, disrupted life tasks (e.g. employment) and social relationships] occur with the decrements in quality of life found in studies of cancer patients. Most relevant are studies with breast cancer patients which provide data linking QoL aspects and immunity. Levy and colleagues (Levy, Herberman, Lee, Whiteside, Kirkwood, & McFeeley, 1990) reported on QoL variables at 3 months post treatment (lumpectomy or mastectomy with or without adjuvant therapy) for 66 women with Stage I or II disease. In addition to estrogen receptor (ER) status predicting NK cell lysis, social support added significantly (+7% of the variance) to the model in predicting higher NK cell activity. These data are generally in line with data from healthy individuals with "positive" indicators of QoL (e.g. social adjustment) predicting higher NK cell lysis and "negative/distress" indicators (e.g. emotional distress) predicting lower.

Data on the health (illness) consequences of stress or data linking the two via immunity are accumulating. One example comes from Cohen et al. (1991). Studying healthy volunteers who were inoculated with either a cold virus or a placebo, they found that rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in psychological stress across five different strains of cold viruses. Data from diagnosed breast cancer groups are relevant. Two studies of extent of disease at initial diagnosis (i.e. number of nodes positive) have been done. Levy (Levy et al., 1985) found self reports of Fatigue (POMS) to be a predictor of nodal status, but there was no effect for Fatigue if NK cell levels were first entered into the regression equation. Levy (Levy, Herberman, Lippman, D'Angelo, & Lee, 1991) examined variables predicting disease free interval (DFI) and recurrence in 90 women with initial Stage I or II breast cancer with data gathered post surgery, and 3 and 15 month follow ups. DFI was predicted by numbers of positive nodes (.-27) and distress (POMS; -.41) at 15 months. Finally, Levy (Levy, Lee, Bagley, & Lippman, 1988) examined time to death following recurrence for 36 women with breast cancer. Along with the medically relevant variables (e.g. DFI), positive affect (Joy) reported at recurrence predicted a longer survival time. In summary, experimental data from stressed but otherwise healthy samples suggest covariation of stress and the incidence of infectious illnesses, and data from cancer samples reveal that conceptually consistent variables are correlated with disease endpoints.

Only three cancer intervention studies have been conducted which have examined immune or health consequences. However, none were, a priori, designed to test disease endpoints, and none included health behaviors in the intervention or the assessment of outcome. The most comprehensive study is that of Fawzy and colleagues (1990 a & b). They studied newly treated Stage I or II melanoma patients randomized to no intervention or a structured short term (10 sessions) group support intervention. Significant psychological and coping outcomes for the intervention subjects were evident by 6 months post treatment; additionally there were increases in the percentage of large granular lymphocytes, the NK cell phenotype, and interferon alpha-augmented NK cell activity. Importantly, the magnitude of the NK changes was frequently greater than 25%. The correlation data was also supportive: interferon-augmented NK cytotoxic activity *increased* with concomitant *reductions* in anxiety (-.37) and depression (-.33). We believe the NK cell data are particularly important because research has shown a reduction in NK cell activity with tumor progression in breast cancer (Akimoto et al, 1986; Takasugi, Ramseyer, & Takasugi, 1977). Also, the intervention effects replicate those of Kiecolt-Glaser et al. (1985) who found relaxation training intervention differences in NK cell lysis for older (primarily female) adults. Six year follow up data on disease endpoints are also available (Fawzy, Fawzy, Hyun, Gutherie, Fahey, & Morton, 1993). Analyses of DFI to death indicate significant group differences, with 29% of controls and 9% of experimental subjects dying in the six year interval. Post hoc analyses indicate

that from baseline to the six month assessment, the survivors reported significant decreases in affective distress, increases in active behavioral coping, and increases in CD16 NK cells and interferon alpha augmented NK cell activity (i.e. immune up regulation). In contrast, those who died showed no significant changes on any of these variables, i.e. no QoL improvement or immune enhancement. Data from a relaxation intervention study provide confirmatory evidence as well. Gruber et al. (1993) studied 13 stage I, node negative breast cancer patients who received EMG biofeedback assisted relaxation training. Assessments during the 9-week intervention indicated significant immune differences between the treatment and control groups in the expected direction. Finally, other relevant data come from Spiegel, Bloom, and colleagues (Spiegel, Bloom & Yalom, 1981; Spiegel & Bloom, 1983) who randomized women with metastatic breast disease to no treatment or a group treatment which met weekly for at least one year. The intervention group reported significantly lower emotional distress (POMS) and fewer maladaptive coping responses than the controls. A ten year follow up (Spiegel, Bloom, Kraemer, & Gottheil, 1989) found a striking survival difference between the groups, 18.9 months for the control subjects and 36.6 months for the intervention subjects from study entry until death.

Purpose of the Present Work (Army Sabatical)

In late 1994 the US Army initiative in breast cancer (1 year sabbatical award for training in psychoneuroimmunology) and research funds from the American Cancer Society (ACS; a two year award and a one year renewal) and were awarded to the PI for preliminary studies and pilot data collection. In the fall of 1994 the sabatical award funded a one course reduction and the PI was able to enroll in the graduate course in Molecular and Cellular Immunology (Dent 513) taught by Professors J. Sheridan and P. Marucha at the Ohio State University. These were the activities funded by the sabatical. Thus, the research funds from the ACS enabled the randomized trial to begin, although every component of the study was significantly under funded. Nevertheless, the monies were maximally stretched to pilot the intervention, hire and train personnel, and at this date (9/1/95), approximately 40 subjects were randomized and completed an initial assessment, with approximately 25 having completed the first follow up assessment (approx. 12 Ss per group). Having completed the immunology coursework, the additional sabatical funds enabled the PI to manage this very large project and also serve as the co therapist for the intervention groups for the trial. The numbers presented in the analyses below will vary somewhat because all data sets are not yet on line. In addition, all assisting units are independently contributing supplies, manpower, and time to achieve pilot data collection. This has been a remarkable effort, however, without significant funding, this project can not be sustained and will end on or about July 1, 1996. Three types of preliminary data are provided.

Table 1: Preliminary summary statistics for selected immunity measures from pilot data on first cohort (N = 36).

Variable	Mean	SD	Variable	Mean	SD
NK Lysis			Monoclonals		
NK 100:1	55.96	26.63	T3	74.59	10.78
NK 50:1	46.11	21.49	T4	49.52	11.42
NK 25:1	34.08	18.67	T8	25.74	8.86
			NK %	18.18	9.93
LAK assay			LAK assay		
IFN γ 50:1	14.74	16.45	IL2 50:1	3.70	7.33
IFN γ 25:1	12.54	15.99	IL 2 25:1	2.14	6.08
IFN γ 12: 1	8.17	11.10	IL 2 12:1	1.68	3.09

First, in **Table 1 above** is data for NK lysis, studies of the ability of NK cell to respond to recombinant interleukin-2 (IL-2) and recombinant gamma interferon (IFN-γ), and the numbers for the monoclonals. These data from the initial assessment indicate that sound immunity values can be achieved at this point in the subjects' treatment histories. The four month followup values from the sample of 25 approximate the initial values and are not significantly depressed from the intervening cycles of chemotherapy that many patients receive. (Of additional note, we have also completed cytokine studies with gamma interferon and tumor necrosis factor. These studies appear to be producing sound values as well.

Second, analyses have been conducted on the relationship between the stress and immunity variables As hypothesized, we found significant negative correlations ranging from -.33 to -.37 (all p's < .05) between stress (either Cohen's Perceived Stress Scale or the Impact of Events Scale) and NK lysis (at all ratios) with the initial assessment data from the first two cohorts (approximately 40 Ss). That is, higher levels of stress are associated with lower NK lysis. A one way ANOVA of the NK lysis using a median split of the sample with either stress score is also significant at all effector to target cell ratios [e.g. median split with Perceived Stress for NK at the 100:1 effector to target cell ratio, $F(1, 33) = 6.90$, $p < .01$].

Third, repeated measures analyses were conducted to document the overall effectiveness of the intervention, even with the small numbers of subjects currently available. For the intervention group, there were significant (all p's > .05) declines in Cohen's Perceived Stress Scale, the Impact of Events Scale, the CES-D measure of depression, and a significant increase in overall quality of life as assessed with the SF-36 ($p < 01$). In contrast for the assessment only group, there were no changes on the stress and emotional distress measures (all p's > .20) nor on the quality of life measure. Finally, there were trends in the area of social contacts, in that the assessment group reported a decline in the numbers of close friends (A: Time 0 = 5.1, Time 4 = 3.5, $p < .09$), whereas the intervention group reported no such negative change (I: Time 0 = 5.9, Time 4 = 5.6, $p > .7$).

These preliminary data document the following: 1) This investigative team can, in a timely and efficient manner, identify, recruit, and bring into both arms of the study sufficient numbers of the target group--women with Stage II or III disease. As is possible with limited resources, all components of the study are operational and trained personnel are in place to achieve collection of psychological, behavioral, immune, medical, and cancer related data. If this study is funded there will be no start up time needed. 2) Reasonable values can be obtained on the immune studies. The absolute level and range of the values are similar to those reported in the PNI literature. 4) We demonstrate the reliability of the stress/immunity relationship found in the PNI literature to this sample of women with cancer. Further, we can demonstrate the specific importance of NK studies in this effort. 5) We document the effectiveness of the intervention in reducing stress and emotional distress and enhancing quality of life as hypothesized with the biobehavioral model; this is a necessary condition for examination of the immunity and disease progression questions. 6) Finally, the PI group has made a substantial commitment to this study, there is considerable institutional support at OSU, the Columbus community is receptive to referral to the project, and a trained and skilled research personnel core is in place.

BODY

Research Design and Hypotheses

Note: Because this is a project that requires future funding, the sections below are written in the future tense.

Overview. We propose a randomized clinical trial (**see Table 2**). Women with stage II or III breast cancer will be randomized within strata to one of two arms: psychological/behavioral

intervention or a no intervention (assessment only) condition. The intervention will consist of two phases; an intensive phase of weekly meetings for four months and a subsequent maintenance phase of monthly meetings for an additional eight months. Our hypothesis is that women being treated with the psychological intervention regimen will show lowered stress, increased QoL, improved health behaviors and compliance, and an increase in immune functioning. And, in turn, women treated with the intervention will show a doubling (ratio of median durations = 2.0) in time to recurrence with a .05 level of significance and power of 0.80, one-sided test.

Table 2: Schematic diagram of the research design for subjects across the 4 years of study participation.

	YEAR 1				YEARS 2-4	
	Dx./Ca. Trt	Follow up (months)			Continued Follow up (months)	
Grp	0	4	8	12	6	12
1	x---------Inten-----x----Maintenance---x----Maintenance--x				x	x
2	x---------None-----x-------None-------x------None--------x				x	x

Note: *Dx.* = Cancer diagnosis and *Ca.Trt.* = Beginning of initial cancer treatment; Inten(sive) = Weekly (x18) intervention sessions with reliability/validity checks on intervention integrity; Maintenance = Monthly (x8) intervention sessions with reliability/validity checks; *x* = Psychological, health behavior, compliance, and immune assessments and disease endpoints.

Rationale for a randomized design of treatment vs. no treatment: An experiment is needed to demonstrate cause-effect conclusions for the intervention in demonstrating immune and health effects. While there is an extensive literature documenting the effectiveness of psychological interventions for enhancing QoL outcomes, an extensive data base does not exist on psychological interventions resulting in enhanced immune responses or health outcomes with cancer patients. There are too few data from too few studies (i.e. N = 3; Gruber et al., 1993; Spiegel et al., 1989; and Fawzy et al., 1990 a &b, 1993) to assert that a psychological intervention can *reliably* alter immune function or health consequences. There are enough data to provide encouragement to proceed, but the reliability of the observation needs further documentation. If we were interested only in psychological and/or behavioral variables as outcomes, selection of a factorial design would be in order as the literature has progressed sufficiently to demonstrate the reliability of psychological interventions for quality of life outcomes. In other contexts, we have urged the study of individual differences or the pursuit of factorial designs when psychological responses are the predicted outcomes (Andersen, 1992). From a statistical standpoint, in psychotherapy outcome research effect sizes for comparison of alternative treatments (e.g. a multicomponent intervention vs. information only vs. no treatment) are small to medium when psychological variables are the outcome, and this requires a doubling or tripling of the sample size to detect differences (Kazdin & Bass, 1989). It is unlikely that immune or health variables would be easier to detect with a factorial or treatment comparison design. Finally, we are hard pressed for evidence for a *particular factor* to manipulate to achieve differential immune responses, although the literature does suggest ones as potentially important (e.g. relaxation, coping, social support; Andersen 1992; Kiecolt-Glaser & Glaser, 1992).

Rationale for using prognostic variables for stratification: Randomization will be stratified by four factors: status of axillary lymph nodes and size of primary tumor for women with negative nodes (3 levels: negative nodes but tumor > 2 cm, 1-3 positive nodes, > 4 positive nodes), hormone receptor status (2 levels: positive vs. negative), menopausal status (2 levels: pre and perimenopausal vs. postmenopausal), and support status (2 levels: spouse/spouse equivalent vs.

none). These disease stratification variables are the ones which best define the high risk breast cancer patient (Clark & McGuire, 1992), and we have a specific rational for each. *Axillary node involvement* is the most important prognostic criterion in breast cancer, and we have categorized node status using the most common groupings used for subgroup analyses (Gelman, 1992). Women with negative axillary nodes represent a heterogeneous group, but we are only including women with tumors > 2 cm because this defines Stage II disease for the node negative woman (Rosen, Groshe & Kinne, 1989). We are also stratifying by *hormone receptor status and menopausal status* as both factors are used to determine treatment and are related to survival. Receptor negative tumors have higher recurrence rates and shorter survival; women with receptor-positive tumors have treatment determined by menopausal status. Other variables were considered for stratification, such as age (Swanson & Lin, 1994) but menopausal status was chosen instead because it functionally stratifies in much the same way and it also influences treatment selection. Finally, a single psychological variable--*presence of spouse/spouse equivalent*--was chosen because of its documented relationship with survival in individuals with chronic illness (e.g. Berkman & Syme, 1979), lower levels of neuroendocrine parameters (Seeman, Berkman, Blazer, & Rowe, 1994), and ease of determination. There are also parallel data for marital status linked to stage, treatment, and survival in cancer patients (e.g. Goodwin, Hunt, Key, & Samet, 1987; see also Bloom & Kessler, 1994 for the importance of marital status as a predictor of psychological morbidity). This stratification factor is also strongly correlated with other sources of support (e.g. financial resources). These latter benefits would be unlikely if we used another psychological measure (e.g. neuroticism, optimism) for stratification. Due to the number of strata, we will use White and Freedman's (1978) minimization method to allocate patients to the treatment groups. As each new subject is entered, a measure of how this patient will affect the overall balance of the study is computed given the patient's combination of prognostic factors. A biased coin, weighted in favor of the treatment with fewer patients, is used to make the assignment.

We chose prognostic variables rather than cancer treatments for three reasons: 1) the prognostic variables define treatment selection; 2) treatment philosophies change; and, 3) prognostic factors predict risk of recurrence and/or survival which are endpoints. It is a standard procedure in small cancer therapy trials to stratify on prognostic variables when the effects of the therapy are small relative to the effects of the prognostic factors. We can not stratify on the variety of treatments available for stages II and III, given sample size constraints. Thus, we have chosen 4 variables which by their combinations will equalize prognostic factors across groups and adjust for potential changes in the "state of the art" in breast cancer therapy over the duration of the trial. We have additionally considered the likelihood that the groups, even when stratified and then randomly assigned, will eventually differ on other "nuisance variables" (e.g. cancer treatments recieved). However, data from Hsu (1989) suggest that the probability that the groups will be nonequivalent on at least one nuisance variable with a total sample size of 200 is less than .0006.

Consideration of the effects of cancer therapies on immune function. We have reviewed the literature on the effect of chemotherapy, per se, on immunity. Some chemotherapies will suppress blastogenesis, but more typically, however, the immune-moderating effects of the majority of cytotoxic chemotherapies are unknown. The issue is further complicated by the influence (and interaction of) other factors which effect immunity, such as the following: (1) drug administration parameters--dose, route, time; (2) antigen administration parameters--dose, route, time; and, (3) host parameters--defense mechanisms assessed, time of assessment, capacity to respond (immunocompetence). Nevertheless, we have examined the available evidence on this issue for the most common drugs used for the women in the proposed research: cytoxin (CY), methotrexate (MTX), and 5-FU which are often used in combination (CMF) and Adriamyacin (ADM), used alone. Among these drugs, CY has been the most well studied. Multiple studies indicate CY consistently causes a sharp reduction in circulating peripheral blood lymphocytes, and lymphoproliferative responses to mitogens are impaired, although the effect on antibody production is more variable and suggests immunomodulation rather than suppression (Ehrke et al., 1989). Other data suggest that high doses of CY are immunosuppressive, whereas lower doses

frequently are immunopotentiating, and data suggest there is recovery of these functions in 2-3 weeks (Grant, Kaesberg, & Eshler, 1991). On the other hand, CY can potentiate both cellular and humoral immune function in animal models, and the available clinical data from humans suggests that CY can augment immune function to clinically relevant antigens in patients with cancer (Ehrke, Mihich, Ber, & Mastrangelo, 1989). Regarding ADM, the most prominent immunosuppressive effect is that it induces meylosuppression, but data indicate that recovery is complete by one to three weeks (Kempf & Mitchell, 1985). Regarding immunopotentiation, augmentation has been found for both cellular and humoral immune responses in animal models, and clinical studies with cancer patients suggest that cellular immune function may be enhanced but the clinical significance remains to be determined (Ehrke et al., 1989). Regarding MTX, some immunosuppression has been found with intermittent administration. Inhibition of blastogenesis has been found after 3-4 weeks of therapy, but it recovers within days with the cessation of therapy; depressed humoral immunity is the most common immunosuppressive outcome of MTX therapy, with less depression of cell-mediated immunity (Grant, Kaesberg, & Eshler, 1991). For 5-FU, the available data suggest some suppression of humoral immunity but rapid (one week) recovery after discontinuance of the drug (Kempf & Mitchell, 1985), with less suppression of cellular immunity (Grant, Kaesberg, & Eshler, 1991). Finally, we note that one of the few studies using a repeated measures paradigm, Levy and colleagues (1985) assessed women with Stage I or II breast cancer a week after surgery and three months later following adjuvant chemotherapy plus radiotherapy or radiotherapy alone. They found a persistently low level of NK cell activity that did not change during therapy. At the same time, the mean levels of NK cell activity were significantly lower for the node-positive women at baseline, consistent with the data cited above regarding lower levels of NK activity in patients with greater tumor burden. Thus, immunologists emphasize that it is the tumor burden (stage) which may be more relevant to NK cell activity than any temporary disregulation caused by surgery, radiation, and/or chemotherapy (Whiteside & Herberman, 1990).

As shown above, our preliminary data indicates that 2 to 4 week interval post treatment (surgery) is sufficient for immune recovery for the majority of women. For women in the study receiving chemotherapy, we are finding that the majority (92%) have completed their chemotherapy (usually 4-8 cycles) by the four month assessment. By the 12 month assessment, all women will have been off therapy for at least two months and potentially for as long as 8 months (with the exception of Tomoxifan). In addition to fully documenting the nature of the regimens for subjects, including radiation and chemotherapy dosages and dosage intensity, we take special care to coordinate blood draws to be as long as possible from the last chemotherapy administration (e.g. 3 weeks), yet not be immediately prior to the next cycle to maximize the likelihood of tapping recovered "baseline" responses yet avoiding acute disregulation with anticipation of (e.g. Jacobsen et al., 1995) or actual drug administration. Finally, Drs. Glaser, Farrar, and Triozzi will provide data from the study on this important topic.

Rationale for the repeated measures (0-, 4-, 8-, and 12-months for year 1 and 6- and 12-months for years 2-4): Multiple assessments are important in year 1 to document the effects of both portions of the intervention. For data analyses in which year in study is a factor, the 4 and 8 month assessments in year 1 will be averaged to achieve a more stable estimate, as the greatest change is anticipated for year 1. This will also achieve uniformity in having 2 assessments for each year when the unit of analysis is year in the study. The repeated assessments will determine the short (< 1 year) and long term (2-4 years) effects of the intervention. Immunity data during follow up will provide prospective documentation of any differential response patterns among those who do and do not recur.

Hypotheses will be tested in three areas. In *Area I, hypotheses involve group differences* on psychological, behavioral, immune, and health outcomes. Specifically, we hypothesize that: (Ia) Intervention subjects will report significantly better psychological outcomes, specifically lowered stress and enhanced quality of life. Intervention subjects will also be less vulnerable to the specific sequelae of breast cancer treatment such as disrupted sexual self concept. (Ib) Intervention

subjects will demonstrate significantly improved health behavior outcomes, including higher rates of positive health behaviors (e.g. physical exercise, lower fat intake), lower rates of negative health behaviors (e.g. alcohol intake), and better compliance with cancer therapy and medical follow up. (Ic) Intervention subjects will have significantly better immune function, as assessed with natural killer (NK) cell responses [e.g. NK cell lysis; ability of NK cells to respond to interleukin-2 (IL-2) and gamma interferon (INF-γ)]. (Id) The intervention group will have better health outcomes, lower rates and/or slower cancer progression. In *Area II we will test the relationships among the variables specified in the biobehavioral model,* including the following: (IIa) the prediction of immune function from the psychological variables (e.g. increased stress is significantly correlated with immune changes, such as decreased NK activity); and, (IIb) the role of the immune variables as a mediator linking psychological/behavioral variables to disease outcomes (i.e. stress is related to decreases in functional immunity which are, in turn, related to shorter disease free interval). *In Area III we will examine individual differences.* We will determine change over time for individuals in each group and test for individual differences related to change in immunity or differential health outcomes. Specifically, we hypothesize the following: (IIIa) We will test whether or not differences between women in their level of social support may moderate psychological or immune responses or health outcomes, e.g. women with greater levels of social support may manifest higher levels of NK activity and/or lower rates or slower disease progression; (IIIb) We will test whether or not differences in personality characteristics might influence vulnerability to lowered immunity or illness progression, e.g. individuals high in extraversion, low in neuroticism, high in openness or high in conscientiousness may have better health outcomes; and (IIIc) Finally, we will examine the medical stratification factors (i.e. nodes, ER/PR, menopause) to determine if the effectiveness of the psychological intervention interacts with them.

Subjects

Eligible patients will be newly diagnosed and/or recently treated (i.e. < 3 months post surgery) women with Stage II or III invasive breast cancer who are ≥ 20 years of age. This is a homogeneous sample in terms of treatments to be recieved and prognosis. Information on line from the CancerNet of the National Cancer Institute documents the estimate of 66% 5 year survival for Stage II and 41% for Stage III. Since these are survival rates, the rates for recurrence will be higher (approximately 50% of the sample will recur in a 5 year interval). Data obtained from the Franklin County (which includes Columbus) branch of the American Cancer Society for 1994 indicated that Stage II and III diagnoses account for 44% of the annual diagnoses in the county. We recruit patients being treated at the OSU Comprehensive Cancer Center (James Cancer Hospital and Research Institute) by the surgical and medical oncology departments, as well as women from the "outside" -- the city and surrounding close communities. We are monitoring the source of referral to the study to see if there are any systematic differences; because of the diversity of routes we are using to solicit women from the outside, there does not at present seem to be a systematic difference. Our goal is to have 3-6 "outside" women per month entered on to the trial to achieve 35-45% of the sample; we presently have 25% in the pilot. Including both OSU and "outside" patients has a significant advantage in that it maximizes generalizability, as virtually all of the psychosocial intervention research has been conducted with only University medical center patients (see Andersen, 1992 for a discussion).

Considering accrual thus far, refusal rates at OSU are currently (9/1/95) running 28% and refusal from outside OSU is 16%. We project an overall rate of 25% (this includes "up front" as well as late refusals, i.e. women who accept initially but later decline prior to the first assessment). The refusal rates in psychosocial intervention studies have ranged from 10 to 25% (Andersen, 1992). In considering the drop out rate, studies of low and moderate risk patients (i.e. Stage I - III: Andersen, 1992) were considered. The literature suggests that dropout rates range from 9% to 27% for the studies which have provided data for initial to 12 month assessments; dropout estimates are not available for longer follow up intervals. For this reason, we will plan for a 25%

drop out rate although our current rate is only 8%. Our power analyses (see Sections E.1 and E.2) indicate that a total N of 200 (100 Ss per group) is needed. Therefore, we will need to identify (i.e. approach for participation) a total of 354 patients when the 25% refusal rate and 25% drop out rate is considered (100 x 2 x 1.33 x 1.33 = 354). At a rate of 10/month, recruiting would extend 35 months. We will, of course, monitor refusal and drop out rates so as to adjust the recruiting time downward or upwards to achieve the target sample of 200 as efficiently as possible.

Experimental Conditions

C.1 Assessment only

Table 2 below displays the schedule for the assessments. Women will be paid a modest fee ($20) for their time and effort for each assessment. These reimbursements will be also used for the women in the intervention condition.

C.2 Assessment and intervention

C.21 *Conceptualization and content of intervention*

The biobehavioral model has been used for targeting of the areas of change. Each construct in the model has been operationalized to correspond to intervention components and assessment measures, shown in **Table 3 below**. Specifically, the intervention includes components to *reduce stress, enhance quality of life (i.e. emotional adjustment, social adjustment and support and breast specific concerns--body image and sexuality), increase positive health behaviors, decrease negative health behaviors, and improve compliance (*see complete description of intervention components is provided below. Briefly, the intervention has two phases. The first phase, the *intensive intervention*, has four parts. Further, we hypothesize that it will be especially important that the psychological intervention produce *long term* behavioral and psychological changes if immune responses and/or disease endpoints are to be affected. Therefore, we include a second phase, a *maintenance intervention,* and the Transtheoretical Model of Behavior Change (Prochaska & DiClemente, 1984, 1986) is used as the guiding theoretical framework for it. This model has been widely used in cancer prevention and screening studies (e.g. smoking cessation, high-fat diets, fruit and vegetable consumption, exercise acquisition, mammography screening; Prochaska et al., 1994). Longitudinal studies of change have found that people pass through five stages of change---precontemplation (no intention to change), contemplation (seriously considering change), preparation (taking steps to change), action (actively involved in meaningful change), and maintenance (maintaining meaningful change)---and further, data suggest that there is a pattern of change in the decisional balance as individuals move through the stages (Prochaska et al., 1994).

Intensive: *Part 1: Stress reduction and enhancing QoL (emotional adjustment)* (Sessions 1, 4-7). There are four components. (a) A simplified version of Gatchel, Baum, and Krantz's (1989) model of stress as a psychophysiological process will be offered as a way to conceptualize the cancer stressor. Adaptive coping strategies (e.g. seeking information, positive appraisal) will be introduced as skills that can be learned and applied generically. (b) Progressive muscle relaxation (PMR) training (ala Bernstein and Borkovec, 1973 and as modified as a skills training effort with group instruction, Carlson & Bernstein, in press) will be used as a method for lowering overall body tension. Women will be provided with cassette tapes for home use. Instruction will begin with 16 muscle group and move through the steps to relaxation by recall. (c) Cognitive restructuring (Hawton & Kirk, 1989) will be used to identify current manifestations of the cancer stressor (e.g. low mood, low energy/fatigue, disrupted relationship with spouse). The A (Activity/Event)--B (Beliefs/Automatic thoughts)--C (Consequences/Feelings and Behaviors) model will be offered with examples. (d) Problem solving will follow the principles of Goldfried and Davision (1976) and Hawton and Kirk (1989). It will consist of five stages: overview of the principles; how to define and formulate target problems, generation of problem solutions; decision

making; and, verification of solutions. To learn the principles, women will have "hands" on experience by working on solutions for two target problems: fatigue and time management. This section will conclude with women targeting 1-2 other areas for problem solving to enhance generalization.

Table 3: Operationalization of the biobehavioral model: Constructs, measured variables, and intervention components.

Construct	Measured Variables	Intervention Components
Stress	Perceived Stress Scale	Rationale (Gatchel, Baum & Krantz's stress model)
	Impact of Events Scale	Progressive Muscle Relaxation training
Quality of Life:		
Emotional adjustment	Distress: POMS	Cognitive restructuring (A-B-C model)
	Mental health: BDI	Problem Solving
	COPE	Positive Coping
Social adjustment	Social and occupational activities	Social network identification (circle model)
	Social network interview	Increasing contacts and/or assistance with network
	Interpersonal Support Evaluations List	Assertive communication skills training
Breast component:	Sexual Experience Scale	Sexuality and menopausal change information
	Body Satisfaction	Body acceptance and sexuality exercises
		Role play of partner communication re: sexuality
Health Behaviors	Positive: Diet, exercise	Diet: Low fat/high fiber information
		Dietary assessment and feedback
		Dietary monitoring and meal planning
		Exercise: Exercise and stress management;
		activity/rest cycling
		Eating and energy balance
		Walking program
	Negative: Alcohol consumption, smoking	Referral info. for cessation and/or self help groups
Compliance	Reports of drug dose; Dose intensity	Disease and treatment information
	Treatment appointment keeping	Communication skills training:
		Interactions with health care providers
	Examination appointment keeping	Goal setting for cancer treatments and followups.
Immunity	NK cell studies	NA
	Cellular immune (T-cell) studies	NA
Disease: Local control	Response to therapy;	NA
	Disease free interval	
Disease: Metastatic	Metastases (Y/N); Time to metastases	NA
	No. and Site(s) of Disease;	
	Disease free interval.	

Intensive: *Part 2: Compliance* (Sessions 2-3, Portions of Session 10). Of the very few studies focused on compliance, the data suggest *information about the disease and treatment* (Richardson et al., 1987; Robinson, 1990), and *enlistment of help of significant others, i.e. social support* (Richardson et al., 1987). There will be three components. (a) Disease and treatment information will be offered to reduce uncertainty and aid in medical decision making and compliance. Existing educational materials (e.g. the NCI's *Breast Cancer Digest* and American Cancer Society materials) will be used. (b) The use of relaxation and distraction in coping with treatments (e.g. chemotherapy side effects) and anxiety vis-a-vis follow up medical examinations will be discussed. (c) Assertive communication exercises will be conducted to enhance communication with physicians and other health care professionals (see below under Part 3).

Intensive: *Part 3: Improving QoL (social adjustment and breast specific component)* (Sessions 8-13). There are four components. (a) The supportive context of the group intervention will be used to direct social comparisons among the group members; as women learn that many of their reactions to the cancer "crisis" are normal and shared by others, problem solving strategies and ways of adaptive coping will be fostered (e.g. Taylor's conceptualization of adjustment to threatening events; Taylor, Lichtman, & Wood, 1984). (b) Women's social network will be identified using a concentric circle model (with the patient at the center). We will systematically cover five levels of social relationships (e.g. coworkers and friends; physicians; parents/in laws and siblings; children of all ages; and spouse/spouse equivalent) and identify sources of satisfaction and clarify areas of difficulty (Cohen & Wills, 1985). (c) Assertive communication skills, modeled after the work of Jakubowski and Lange (1978) will be taught to assist women in expressing their thoughts, feelings, and needs in a manner which facilitates support from and communication with members of their social networks. Four techniques are used: specificity and clarity of one's message; direct communication; "owning" one's message (use of "I," "my" etc. in statements); and, asking for feedback. These skills will be practiced across the five levels of social relationships identified in (b) above. (d) Specific breast cancer sequelae of *body changes*, menopausal changes, hormonal changes with Tomoxifan therapy, and impact on sexual self schema (esteem) will be discussed as well as coping with sexual changes as discussed in Andersen and Elliot (1993). This session will be prefaced by a session focused on social support from the partner.

Intensive: *Part 4: Health behaviors,* (Sessions 14-17). There are three components: diet, exercise, and negative health behaviors. (a) Information on a low fat eating plan will be offered to achieve dietary change (dietary fat $\leq$ 25% of energy intake and dietary fiber of 20-30 grams/day from fruits, vegetables, and grains; these are NCI fat and fiber guideline levels). The intervention will provide participants with the skills and knowledge to gradually lower their fat and increase their fiber intake, and was adapted from the procedures from the WINS study. The guidelines emphasize the influence of discriminative stimuli for eating, the substitution of low-fat food items for high fat foods, and the setting of step-wise goals for lowing fat intake. The guiding conceptualization will be that of health behavior change rather than dieting. We will begin and end the dietary intervention with individualized, stage matched reports for dietary change (i.e. fat reduction and specific fiber recommendations based on current eating pattern). Such reports are generated by incorporating the data from the stages of change (Prochaska et al., 1994), Decisional Balance (Janis & Mann, 1977), and the Food Frequency Questionnaire (Kristal, SeLett, Henry, & Fowler, 1990; see below). Recent data demonstrate that messages individually tailored to an individual's stage of change generated a significantly greater reduction in dietary fat intake than non-tailored messages based on NCI Dietary Guidelines (Campbell, DeVellis, Strecher, Zimmerman, DeVellis, & Sandler, in press; Greene, Rossi, Geed, Willey, & Prochaska, in prep). Consultant Geoffrey Greene has developed these procedures and will provide the computer software for generating the reports. Finally, we note that if the dietary data indicate deficiencies in RDA nutrients based on 2/3 of the 1989 RDAs (Food and Nutrition Board, 1989), women in either group (intervention or control) will be provided with appropriate educational materials to increase intake of the deficient nutrient(s). Study subjects will be monitored by project dietary research

assistant supervised by co PI Bossetti. We will monitor women with significant weight loss, a low albumin, or other indicators of compromised nutritional status to ensure that there is appropriate medical and dietary coverage, and to ensure that the dietary intervention is complimentary to any other dietary care which is needed.

(b) According to the American College of Sports Medicine's (1991) Guidelines for Exercise Testing and Prescription, "exercise therapy is becoming an accepted aspect of rehabilitation in patients with cancer. Regular exercise counteracts the detrimental effects of bed rest and provides psychological benefits " (pg. 178). Available data suggest that resuming or maintaining regular exercise would provide positive health benefits, as recent controlled trials suggest that even moderate levels of aerobic exercise performed 3-5 times per week for 20-30 minute intervals improve aerobic fitness in middle aged women (King, Haskell, Taylor, Kraemer, & DeBusk, 1991). In the only study that assessed the effect of aerobic activity in breast cancer patients, MacVicar et al (1989) reported that exercising on a stationary bicycle three times per week was associated with a 40% increase in aerobic efficiency and fewer reports of nausea than in non-exercise controls. The exercise intervention is modeled on the home walking protocol of King (1991) et al. which was found effective for older women. An exercise program of this magnitude (producing 50-60% of maximum heart rate) is sufficient to produce positive psychological benefits (King, Taylor, & Haskell, 1993), and low-intensity exercise appears to be beneficial for the immune system in terms of increasing the numbers of natural killer cells and the number of circulating lymphocytes (Newsholme & Parry-Billings, 1994). Didactic information will include how to set realistic goals, schedules for rest, techniques for increasing energy expenditure during activies of daily living, and coping strategies for setbacks. Women who are unable to perform the walking protocol due to treatment complications will be provided with alternative activity/rest goals. Co-PI Emery will provide guidance on the specific procedures for implementing and monitoring the exercise program.

Prior to participation in the exercise component, subjects will complete the Physical Activity Readiness Questionnaire (British Columbia Department of Health, 1975). This instrument was developed as a screening instrument and tested with over 1 million Canadians for the Canadian Home Fitness Test. It is 100% sensitive for the detection of medical contraindications to exercise and approximately 80% specific. In addition, co-PI Farrar will provide medical clearance for all subject's, and will provide medical consultation during the course of the study for any questions or concerns regarding excercise participation of subjects.

(c) Information on *controlling negative health behavior*s (i.e. alcohol consumption and smoking) will be provided along with specific referral to community/self help group resources. *Disturbed sleep patterns* will be addressed with recommendations regarding activity programming, relaxation training, and sleep pattern monitoring.

Maintenance: *Part I: Preparation for maintenance (Session 18, Intensive).* To implement the maintenance plan, immediately prior to the final session of the intensive intervention, each woman will complete two measures: 1) Stages of Change: Following the procedures of Prochaska et al. (1994), a 4- or 5- item algorithm for determining the stage of change for the seven target areas which have been the main foci of the intensive intervention: relaxation training, adherence to medical therapy, social support, sexuality/body image, diet, exercise, and control of a negative/problematic health behaviors. For example, the first item on the algorithm will ask a woman if she has engaged in the desired positive behavior (e.g. practicing relaxation three times per week for 20 minutes; exercising 20 minutes three times per week; having one-two face to face interactions with a confidant per week). If a woman reports the undesired status or does not intend to change in the next 8 months (the length of the maintenance period), then she will be in the precontemplation stage. If she intends to change in the next 8 months, she will be in the contemplation stage. Women in the action stage will have reached a particular criterion (e.g. practicing relaxation three times per week) within the past 4 months (the length of the intensive

intervention, or the relevant interval since the intervention was conducted during the intensive period). At this first assessment it is unlikely that any women will be in the maintenance phase (usually defined by maintaining the criterion behavior for six months).

2) Decisional Balance: Women will complete decisional balance measures (Janis & Mann, 1977) for each of seven specific target areas: relaxation training, adherence to medical therapy, social contact with an identified target, sexuality/body image, diet, exercise, and control of a negative/problematic health behavior. These measures will be brief (e.g. 8 item) measures which will tap the eight categories of decision making in the Janis and Mann model: gains or losses for self, gains or losses for significant others, self-approval or self-disapproval, and approval or disapproval of others. For each measure the item content will be specific to the target area. Following the method of Prochaska et al. (1994) a 5 point Likert scale will be used that ranges from *not important* (1) to *extremely important* (5) or *strongly disagree* (1) to *strongly agree* (5).

During the first portion of the last intensive therapy session the measures will be scored by research assistants. A brief, individualize report will be prepared for each woman which will summarize the level of the stage of change (i.e. precontemplation, contemplation, action, etc.) for each of the target areas. The report will be further individualized by providing stage-specific and target-specific intervention information for each women, modeled after the work on individualized self-help interventions of Prochaska et al (1993). The session will begin by delivery of the reports to the women, with discussion of the stages of change model and its applicability to the intervention targets. The session will end by establishing target goals in each area for each woman.

Maintenance: Part II: (Sessions 19--26). The same general format will be used for the eight maintenance sessions. Six primary components will be included. (a) We will review the goals for the month, with each woman rating goal attainment and updating her current progress, vis-a-vis stage of change (e.g. determine whether she has moved from contemplation to action). (b) We will emphasize problem solving, social support seeking, and increasing awareness of cues (including self talk) as these general strategies, along with duration of therapist contact in a maintenance program (e.g. Perri et al., 1988), have been important in the maintenance of change (e.g. Urban, White, et al., 1992). (c) Each session we will revisit intervention strategies for one of the seven target areas: relaxation training, adherence to medical therapy, social support, sexuality/body image, diet, exercise, and control of a negative/problematic health behavior. However, this additional coverage of target areas will be broken down into stage specific interventions, i.e. brief modules on relaxation for precontemplators, relaxation for contemplators; relaxation for maintainers, etc. During the session the women will divide into small groups based on their respective stage of change for the target behavior and the interventions will be delivered within the small groups and stage appropriate exercises and written material will be provided. Given the previous intensive intervention period, it is likely that the women will fall into only 2 or 3 groups--contemplation, action or maintenance. With two therapists it will be possible to assist all the subgroups during this segment. (d) The session will close with goal setting for the next month. e) We will prompt the group members to maintain contact with one another between the monthly sessions. For example, women have been comfortable with sharing telephone numbers or some members pair up as "buddies" for bi-weekly contacts. These contacts are for social support and to facilitate maintenance of the behavior change goals. f) Crisis management will be needed for particular difficult situations which arise (e.g. local recurrence, death of a family member). The group will need to process such experiences and provide support to one another as is appropriate.

C.22 *Therapists and therapy reliability*

A single cycle will be 26 1.5 hour sessions (18 intensive + 8 maintenance) for a total of 39 therapy hours. At least ten cycles of the intervention (i.e. 100 intervention subjects/8-12 subjects per

group) will be conducted. Several steps will be taken to insure reliability of the treatment procedures. First, to maximize similarity across cycles, the therapists (two per group) will follow a session-by-session written manual (The manual is available on request). To insure reliability within intervention cycles, therapist teams meet weekly to review the previous session, rate the topic coverage, and prepare for the next session. Further, all sessions will be videotaped and independent ratings of 50% of the intensive and 100% of the maintenance sessions will be done. If there is "drift" in the nature of the intervention, we will take corrective action immediately. These tapes will also provide an opportunity to quantify the involvement of the subjects in the intervention--a critial component of process research--to generate testable hypotheses of intervention components.

Second, steps will be taken to standardize and document the treatment "dose" to the women. 1) Attendance [both in session and "at home," see description below] will be monitored. 2) Each woman is given an intervention notebook which provides an easy to read written summary of each session. This facilitates the women keeping focused on the sequence and content of the intervention and, often, women use the session descriptions to prepare for the next week's session. 3) Women will be absent on occasion (e.g. women on chemotherapy often have low counts or feel ill) and we have devised procedures for them. When a session is missed, a woman is telephoned by the primary therapist. The therapist provides an update to the woman about the status of the other group members and then together they discuss the session's content as provided in the notebook (The notebooks are written as if a therapist is talking to an individual person). The telephone call is usually 15-20 minutes. This procedure keeps a woman up to date on the group progress, ensures that minimal group time is needed for "catch up, " and reduces the dropout rate as the women stay engaged in the group activities. We are currently pilot testing a checklist to document the content and process of these telephone calls (see Nail, Greene, Jones, & Flannery, 1989 or Hagopian & Rubenstein, 1990 for examples). 4) We will assess the womens' perceptions of the group experience with a modified version of the Participant Rating Form from the GROW Project (Roberts et al., 1991). It contains 30 Likert items and asks women to rate the most important aspect of the group experience. 5) For all subjects, we will document participation in any therapeutic, counseling or related activities. This brief assessment will occur on an annual basis, and we will obtain descriptive data on how involved the woman is/was in these experiences and how supportive she found them, attendance, and the type of group (e.g. breast cancer, cancer general, therapy group, social/recreational, religious group).

We also have procedures in place in the event a woman's disease recurs during study participation. There are at least four circumstances to consider. 1) Some women may be initially regarded as stage II or III disease but are quickly "restaged" following the initial assessment but prior to the four month assessment. The typical scenario for this rapid change is that such women have many positive nodes (e.g. 10+) and further studies are being done for screening prior to bone marrow transplant; during the course of such studies, disseminated disease (e.g. lung, liver or brain mets) may be found. This situation has arisen once in 12 months of recruiting. Our procedure is to provide supportive individual psychosocial monitoring and referral to other psychosocial services when and if the woman has desired such; women in the intervention condition stay in the intervention group if they so desire. 2) If disease recurs for a woman during the course of the intervention interval, either the intensive or the maintenance phase. When this has occurred for women in the intervention condition, they have continued to come to the intervention sessions as their health has allowed. Whether or not they come, all group members are informed of the situation, and if they feel comfortable doing so, they are urged to contact the woman. Because we anticipate this happening, we will make every effort, and have been successful thus far, to keep the intervention "open" to everyone, regardless of the immendiate disease status. We have found that topics such as stress management, social support, body image, diet, compliance, etc. are important as well for women with recurrent disease. 3) Regardless of when the recurrence happens, we have identified a "paired-down" core assessment battery should a woman wish to limit her participation and/or her energies are limited. Some women will want to discontinue their

participation entirely upon recurrence, but to date, women do not want to drop out and they are continuing their involvement as long as they feel it reasonable.

Measures

D.1 Stress

D.11 ***Perceived stress.*** The Perceived Stress Scale will measure an individual's appraisal of their life as stressful and includes items for perceptions of daily life as unpredictable, uncontrollable, and overloading. These dimensions are of particular interest for women undergoing difficult, lengthy therapies in the midst of family, home, and job responsibilities. This measure is a predictor of symptomatology beyond that due to depression (Cohen & Williamson, 1988) and norms are available for middle and older age adults.

D.12 ***Traumatic stress.*** The Impact of Events Scale (Horowitz, Wilner, & William, 1979) will examine intrusive and avoidant thinking about the cancer stressor. The 15 item questionnaire has two distinct factors: avoidance and intrusion ($r = .42$); internal consistency is .82 and .78 and two-week test-retest is .79 and .89, respectively. The continuing psychological impact of breast cancer is well documented (e.g. Taylor, Lichtman, & Wood, 1984), and individuals who experience involuntary, distress-related ruminations following traumatic life events are also those who appear to suffer the greatest negative effects.

D.2 QoL: Emotional adjustment and coping

D.21 ***Emotional distress.*** The Profile of Mood States (McNair, Lorr & Droppleman, 1971) will be used. It is a 65-item self-report inventory which asks the subject how she has felt during the past week and yields measures of six mood subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Internal consistency for the scales range from .83-.93. This is one of the best measures of transient mood states. This measure has been widely used in cancer research and been sensitive to immune changes and pre to post treatment differences (e.g. Andersen, Anderson, & deProsse, 1989b).

D.22 ***Mental health*** will be assessed with the Beck Depression Inventory (BDI). This 21 item measure assesses mood, physiological or vegetative signs of depression, and cognitive aspects. Although syndromal depression is expected to be rare among women in the proposed study (Massie & Holland, 1990), depressive symptoms are frequent and clinically important. BDI subscale scores can be calculated for somatic and psychological items. Correspondence between conventional BDI cutoff scores for syndromal diagnoses (i.e. < 11, non depressed; 11-16, mildly depressed; and > 16, moderately to severely depressed) have been excellent in studies that have used RDC criteria, including two studies with ambulatory medical patients (Nielsen & Williams, 1980; Rapp et al., 1988). Thus, the BDI will provides an efficient assessment of the severity of depressive symptoms.

D.23 ***Coping.*** At present the biobehavioral model does not specifically identify a coping construct. However, the literature on breast cancer would suggest that coping strategies may moderate emotional adjustment processes (see Carver, Puzo, 1993). For this reason, the 24-item short version of the *COPE* (Carver et al., 1989) will be used to provide preliminary data on differential coping responses across time. The COPE is a broad band measure, assessing such strategies as problem focused ones (e.g. active, planning), use of social support, turning to religion, substance use, as well as more problematic efforts (e.g. denial, disengagement). Use of the scale with women with breast cancer indicates satisfactory test-retest reliability (.65 to .90) and specific strategies (e.g. acceptance) predicting emotional distress longitudinally (Carver, Pozo et al., 1993).

D.3 QoL: Social adjustment

D.31 ***Social and occupational activities*** will be assessed with a modified version (see Andersen, Anderson, & deProsse, 1989b) of the Katz Social Adjustment Scales. It is a 25-item inventory composed of five factors (73% of the variance): child and home activities (5 items), social contacts with friends (4 items), contacts with relatives (3 items), recreational activities (7 items), and employment involvement (5 items). Rather than perceptions or satisfaction, behavioral frequencies of these activities are obtained. Internal consistencies range .68 to .95 and the measure is sensitive to short (4 months) and long term (12 months) recovery from cancer (Andersen, Anderson, & deProsse, 1989b).

D.32 ***Social Network.*** The Social Network Index Interview (Cohen, 1991) will assess social integration and is potentially less subject to mood-related biases than perceptions of support. This measure assesses the number of people with whom the individual had contact with on a regular basis and the number of important roles fulfilled by these supports (e.g. spouse, parent, child, employee, friend, neighbor). The number of roles and the number of relationships across roles are predictors of mortality in epidemiologic studies (e.g. Berkman & Syme, 1979; House et al., 1982). Internal consistency is .65.

D.33 ***Social Support.*** The Interpersonal Support Evaluations List (ISEL; Cohen et al., 1985) contains 40 questions and responses range on a 6 point scale (1 = I agree very much, 6 = I disagree very much). The ISEL measures the perceived availability of the following support resources: (1) appraisal, the availability of some one to talk to about problems, 2) tangible, the availability of material aid, 3) belonging, the availability of people to do things with, and 4) self-esteem, the availability of a positive comparison when comparing the self with other. Cohen et al. (1985) report that the internal consistency of the scales range from .60 to .92, and the scales are not overlapping (.24, ns). A four week test-retest reliability is .87 for the total scale.

D.4 QoL: Breast specific component

D.41 ***Sexual activity.*** The short form of the Sexual Experience Scale will assess the range and frequency of current sexual activity. The inventory includes 12 items which are rated on a 9 point frequency scale. The measure includes five factors: intimate non intercourse activities (two factors), intercourse, anal stimulation, and masturbation. Internal consistency is .84 and 4 month test-retest reliability is .72. Items are worded appropriately to assess both heterosexual and lesbian relationships. The measure is sensitive to change from sexually disruptive breast cancer treatments (e.g. Andersen & Jochimsen, 1985).

D.42 ***Body Satisfaction.*** The 10-item version of the Body Satisfaction Scale will be used to assess satisfaction with the physical body. The short form assesses two satisfaction dimensions: general facial and sexual body (breasts, genitals) and weight and its body correlates for women--hips, thighs, and buttocks (Andersen & LeGrand, 1991). Internal consistency reliability is .76. Data from women with breast and gynecologic cancer indicates that the measure is correlated with conceptually relevant aspects of sexuality, such as sexual desire (Andersen & Jochimsen, 1986; Andersen & LeGrand, 1991).

D.5 Health behaviors

D.51 *Diet*

D.511 *Dietary reports: Telephone recalls.* We will use the validated data collection procedure developed for the WINS protocol (WINS, 1993), four unannounced telephone recalls will be collected from all participants at baseline to determine fat intake. Recalls will be collected on non-consecutive days during a two-week period, and will include two

weekdays, one Saturday and one Sunday. Average daily nutrient intake will be calculated using the following algorithm: average daily nutrient intake = {[(Weekday 1 + Weekday 2)/2] x 5 + Saturday + Sunday}/7. If the baseline dietary data indicate deficiencies in RDA nutrients based on 2/3 of the 1989 RDAs (Food and Nutrition Board, 1989), participants in both groups will be provided with appropriate educational materials to increase intake of the deficient nutrient(s). This same format will be used for the follow up assessments to monitor both adherence and nutritional adequacy. Telephone assessments are the current "gold standard" in dietary assessment and of the software programs available, the Minnesota Nutrition Data System (NDS) software package is the most accepted. The University of Minnesota began development of the NDS in 1976 to assess the dietary habits of subjects enrolled in the Multiple Risk Factor Intervention Trial (MRFIT) and the Lipid Research Clinics Primary Prevention Trial. A customized version of the NDS is being used in the National Health and Nutrition Examination Survey (NHANES III) to collect dietary data from more than 30,000 Americans. The package to be used will provide calculations for 32 nutritients and 9 nutrient ratios.

D.512. *Dietary patterns*: The Food Frequency Questionnaire (Kristal, Shattuck, & Henry, 1990) will be used as a self report measure of dietary patterns related to selecting a low fat diet. Additional items used by Green, Rossi, Reed, Willey & Prochaska (in press) will be included to assess selection of high fiber foods. The 18 item scale has test retest reliability of .87 and internal consistency of .62, appropriate for a measure which taps four dimensions of dietary behavior (i.e. excluding high-fat ingredients, modifying high fat foods, substituting low fat foods, replacing high fat foods). This measure will be used to generate the stages of change individualized reports on dietary change.

D. 52 ***Exercise.***

D. 521 *Seven-Day Physical Activity Recall* Questionnaire (Blair, 1984). This measure was developed as a community health survey as part of a CHD community prevention study (Stanford Heart Disease Prevention Program). It is administered by an interviewer in 10 to 15 minutes, and co-PI Emery will provide training of the procedures. Raw data from the interview are used to calculate total energy expenditure, including exercise and leisure activities. Normative data from age similar women are available.

D. 522 *Self reports*. Two questions from Washburn, Adams, & Haile (1987) will also be included to assess: (1) subjects self-rating of activity level compared to peers, and (2) days per week of exercise-induced sweating. Validity for these two items was established by comparing responses to the items with measurements of resting heart rate, triceps skin folds, and self-reported physical activity, suggesting that this simplified approach provides a useful index of physical activity.

D. 523 *The Baecke* et al. (1982) questionnaire regarding exercise and physical activity during leisure time provides information about habitual physical activity. The questionnaire has adequate reliability (.74 to .88) and was previously used by King et al. (1991).

D. 524 *The Minnesota Leisure Time Activity (LTA) questionnaire* (Taylor et al., 1978) will provide an assessment of exercise activity changes during the course of the study. The questionnaire was developed for use in longitudinal studies of coronary heart disease, including the Multiple Risk Factor Intervention Trial (MRFIT; Paul, 1976). The questionnaire will be modified to assess only activity between assessments.

D.53 ***Smoking.*** At baseline we will obtain information on lifetime use of tobacco products, including age of onset of use, periods of abstinence of greater than one month, and amount currently used. From these data, quantity and duration of use of each product will be calculated. Dose of current use will be calculated using the following equivalencies: 1 tobacco unit

= 1 cigarette = 0.2 cigars = 0.4 pipefuls. Follow up smoking reports will be obtained with the telephone recalls.

D. 54 ***Alcohol use.*** An assessment similar to that for smoking will be done for alcohol. At intake, subjects will be asked about the date of the last alcoholic drink, and single items will assess the age of onset of use, current frequency (e.g. days/week and weeks/year), amount (e.g. drinks/day, and ounces/drink), and type (e.g. beer, wine, and or liquor) consumed. Dose is calculated using the following equivalencies: 1 alcohol unit = 1.5 oz. liquor = 12 oz. beer = 6 oz. wine. At baseline, subjects will also complete the Mischigan Alcoholism Screening Test (MAST) which is the psychometrically strongest screening measure currently available (Mischke & Venneri, 1987). Internal consistency for the 24 self report items is .84 and the measure is capable of making DSM-IIIR distinctions between a range of problem drinkers (Ross, Gavin, & Skinner, 1990). Follow up alcohol use reports will be obtained with the telephone recalls.

D.6 Compliance

D.61 ***Reports of oral drug dose.*** We will administer the Morisky et al (1986) brief interview (4 questions) measure of oral medication adherence (e.g. Tomoxifan). Despite its simplicity, this measure is internally consistent (.61), has concurrent validity (e.g. predictive of drug blood levels), and has predictive validity (e.g. predictive of compliance 2 years post assessment).

D.62 ***Calulations of dose intensity.*** A sensitive measure of cancer (chemo) therapy when different treatment regimens are being compared is dose intensity, which has been defined as the amount of drug delivered per unit time, expressed as mg/m^2/wk, regardless of the schedule or route of adminestration (Hyrniuk, 1988). Relative dose intensity (RDI) is the amount of drug delivered per unit time relative to an arbitrarily chosen standard for a single drug, or, for a combination regimen, with the decimal fraction of the ratio of the test regimen to the standard regimen. To compare the dose intensity of combinations of drugs, the average dose intensity of the combination is calculated as the average amount of drugs delivered per unit time compared to an arbitrarily chosen standard. To calculate average RDI for a regimen containing fewer drugs than the standard regimen, a dose intensity of zero is assigned to the missing drug(s), and the average RDI of the test regimen is divided by the total number of drugs in the standard. The dose intensity of various protocols is compared over whatever time frame the treatment protocal is administered . Calculations can be made of intended dose intensity, the dose intensity as described in the treatment protocol, and actual or received dose intensity. Received dose intensity reflects the impact of dose reductions and necessary treatment delays imposed in actual practice because of toxicity and is thus the more important data. Since calculations are made on the basis of the amount of drugs given per week regardless of schedule, treatment delays are given equal weight to dose reductions.

These data are important, as a clear-cut relationship between dose intensity and response rate has been demonstrated in breast cancer (e.g. Bonadonna & Valagussa, 1981). Also, these data are needed to document the magnitude of differences, if any, between cancer treatments planned and administered to women in the different arms of the study. They will also be examined to determine if psychological distress, per se, or involvement in the intervention arm may have been correlated with higher levels of therapy (greater dose) actually received when compared to the level of cancer treatment planned.

D.63 ***Appointments for treatment delivery and follow up.*** The number of missed treatment delivery appointments (e.g. failing to appear for chemotherapy administration or radiotherapy treatments) will be recorded (i.e. total number as well as percentage of total appointments). We will also record relevant data effecting treatment delivery, such as medically recommended delays (e.g. a radiation therapy "hold" because of skin irritation). We will record the number and percentage of follow up visits which were kept. For most physicians,

standardized schedules (every three months) exist to facilitate this assessment.

D.7 Immune studies and supplementary laboratory studies

Approximately 60cc of blood will be obtained from each subject at each assessment. By obtaining four blood samples the first year and two per year thereafter, we will monitor the breast cancer patients during the time when risk for recurrence is highest. We attempt to sequence study draws with medical follow up draws, but this schedule is often not possible. The blood samples will be treated with heparin or EDTA to prevent clotting. Mononuclear cells will be separated using Hypaque-Ficoll density gradients, washed 2 times with Mg and Ca-free buffer, counted in a Coulter Counter, then used as described below. We will use fresh cells to perform all the cellular assays and will attempt to control for laboratory variability in the assays by using the same lot of media, the same lot of fetal bovine serum (FBS) or human pooled serum, the same lot of plastic tissue culture plates, etc. and, when possible, the same technicians performing the same assays on an annual basis. These and other standardizing efforts (e.g. single preparation of media, volume purchase of FBS and plastic ware) are routine in the Glaser laboratory. While these practices are not the same as performing all assays on one day with all the same reagents, they control for many of the important variables, and these practices have been satisfactory in prior studies from the OSU PNI laboratories.

Other laboratory studies will also be done. *Complete blood cell counts (CBC) and differentials,* performed by the Clinical Immunology Laboratory at the OSU hospital, will be obtained on each blood sample. Lastly, we monitor nutritional status with concurrent *serum albumin.* If this marker is out of the normal range, then the subject's immunological data for that draw is excluded. In the past ten years of PNI studies at OSU we have rarely found subjects who have abnormal levels, but occurrence may be more common with cancer patients.

D.71 ***NK cell numbers.*** We will determine the percentages of CD3+, CD4+, CD8+ lymphocytes and NK cells by flow cytometry using the appropriate monoclonal antibodies (Coulter) and using routine procedures in the FACS Laboratory in the James Cancer Hospital. Having both the CBC and differential data, along with the percentages of these cell populations, we will be able to determine the absolute numbers of lymphocytes and NK cells. Quantitative data on the NK cells is needed to aid in the interpretation of the NK cell activity studies (see below); this will enable us to determine whether any difference in activity is a result of function or NK cell numbers.

D.72 ***NK cell lysis.*** As discussed in the Background section, we will study NK numbers and function, and test if NK numbers and their ability to kill target cells is differentially lower in the assessment subjects compared to the intervention subjects. This protocol has been previously reported (Glaser et al., 1986). Briefly, cells will be prepared to make a 50:1, 25:1, and 12.5:1 effector to target cell ratios and will be seeded in triplicate, in 96-well microliter plates. Additional wells containing only target cells (K562) in medium or target cells in a medium containing 1% sodium dodecyl sulfate will be used to determine spontaneous and maximum release of radioactivity, respectively. Plates will be incubated for 4 hours in a 5% CO_2 incubator at 37°C. Supernatant will be harvested using a Titertek Supernatant Collection System and activity will be determined by the release of ^{51}Cr into the supernatant. Supernatant will be counted using a Beckman 9000 gamma counter.

D.73 ***Ability of NK cells to respond to recombinant IL-2 and recombinant IFN-γ.***

Of added relevance are studies on the ability of the NK cells to respond to interleukin-2 (IL-2) and gamma interferon (IFN-γ). These studies were chosen because NK cell activity can be enhanced in cancer patients using cytokines like IL-2 to induce LAK cells and IFN-γ. Also, differences exist in

the ability of NK cells to respond to IL-2 and IFN-γ in cancer patients managed with different types of therapy, i.e., local radiotherapy alone or radiotherapy plus adjuvant chemotherapy (Akimoto et al., 1986). We might anticipate that if the intervention is effective in lowering stress, then intervention subjects' NK cells might be more responsive to IL-2 and/or IFN-γ than NK cell responsiveness in the control group.

Peripheral blood leukocytes containing NK cells will be prepared as described above. Cell suspensions will be prepared, 2.8 x 10^6/ml, in complete RPMI 1640 medium supplemented with 10% FBS. The cells will be incubated with either media (control) or recombinant IL-2 (60 units/ml) (Genzyme) or IFN-γ (250 units/ml) (Genzyme). The cell suspensions will be gently mixed and incubated at 37^0 C for 65 hours. The concentration of lymphokines added is based on studies in the Glaser laboratory (Glaser et al., 1991). Following incubation, lymphocytes will be washed 3 times in RPMI 1640 medium containing 10% FBS in order to remove residual cytokine. An NK cell assay will then be performed as described above.

D.8 **Health status**

D.81 ***Cancer treatment toxicities.*** The SWOG (Southwest Oncology Group) criteria will be used to document the types of and severity of toxicity reactions from any of the cancer treatment regimens, particularly chemotherapy. The standard categories (e.g. blood/bone marrow, gastrointestinal, liver, kidney and bladder, heart, blood pressure, neurologic, fever, metabolic) are included with specific descriptions for each rating (0-4). This assessment will be conducted by the CRC nurses who are trained and skilled in toxicity assessments.

D.82 ***Functional performance status*** will be assessed using the Karnofsky Performance Status Scale (Karnofsky & Burchenal, 1949) which is the most widely used measure of functional status in cancer studies. The scale ranges from 100 (Normal, no complaints, no evidence of disease) to 0 (Dead) with each decile defined (e.g. 70 = Cares for self, unable to carry on normal activity). Across cancer studies interrater reliability for the scale ranges from .70 to .97, and many studies have demonstrated predictive validity with significant and high correlation with cancer endpoints (e.g. death, treatment toxicities, etc; Ganz et al, 1988). The CRC nurses will do this rating.

D.9 **Other data/measures**

D.91 ***Social desirability*** will be assessed with the 13-item short form version (Reynolds, 1982) of the Marlow-Crowne Social Desirability Scale. High scorers tend to describe themselves in unrealistically positive ways on self-report measures. We will administer the short form at the annual assessments as a strategy for examining this bias in the self report data, particularly for emotional distress as there is suggestive evidence for such a bias in older adults (Aneshensel et al., 1987).

D.92 ***Individual differences (personality).*** The Goldberg (1992) factor markers will be used to assess Extraversion, Neuroticm, Openness (Intellect), and Conscientiousness. For each factor, 20 unipolar trait adjectives are used and each is rated on a 9 point scale as to how inaccurate vs accurate the word describes the rater. Extensive psychometric analyses of this measure have been done (Goldberg, 1992) including replications of the factor structure (e.g. coefficients of congruence range from .93 to .99), coefficient alpha reliability (ranging from .88 to .97), and correlations with Costa and McCrae's NEO-PI (ranging from .46 to -.68 with the domain scales). Finally, this measure is easier and quicker for subjects to complete than the NEO-PI.

Data Analyses

E.1 Statistical Power Analyses

Effect sizes for variables of primary interest were estimated using data from previous cancer and PNI studies of the investigator group, meta analyses of effect sizes for depression and immunity (Herbert & Cohen, 1993a) and stress and immunity (Herbert & Cohen, 1993b), and other relevant studies. For the immunity outcomes, NK lysis is used as the primary measure for power analyses described below. All analyses that follow are based on a desired power of approximately .80 and at least an alpha level of .05 or lower. Given the directional nature of the hypotheses and the support for these specific predictions in the literature (e.g. Herbert & Cohen, 1993 a & b), power calculations were based on one-tailed tests.

E.11 ***Effect size between psychological and immune variables.*** We are interested in the prediction of immune function (NK cell lysis) from the psychological (stress) variables (see Figure 1 in Addendum). We considered Herbert and Cohen's (1993a, see Table 3) meta analysis of depressed mood and immunity. It provides a mean correlational effect size of -.182. (Depressed mood would be appropriate for the study sample, in contrast to diagnoses of clinical depression.) The projected total sample size of 200 would yield statistical power = .79 for detecting an effect of this magnitude. This association was the weakest of the effects of primary interest (see below), and 200 Ss provide adequate power to detect this effect. We also considered the relationship between stress and immunity and examined the data in Herbert and Cohen's (1993b; Table 1) meta analysis. It provides a mean correlational effect size of -.283 for stress and NK cell activity. For detecting an effect of this size, the projected sample size of 200 would yield statistical power > .99. Additional meta analyses of specific stressor characteristics and NK cell activity provide even more favorable effect size estimates: associations between long term stressors and and NK cell activity provide correlational effect sizes of -.664, and stressors with interpersonal components yield effect sizes of -.544 (Herbert & Cohen, 1993, Table 1). Both of the latter qualities--long term and interpersonal components--are relevant to the breast cancer stressor. If effect sizes are within these ranges with N = 200, power is > .99.

E.12 ***Effect size between psychological intervention and immune variables.*** Analyses of the Kiecolt-Glaser et al. relaxation intervention study indicate that a total N of 45 (15 Ss in three groups) was sufficient to detect a 15% increase in NK cell lysis in the intervention group compared to a no treatment control. Based on the difference between the means (baseline vs. end of intervention), the scaled mean difference effect size was calculated as being .53 (equivalent to a correlational effect size of r = .26; Cohen, 1988, pg. 23, equa 2.2.6). If a similar effect were present in the proposed study, a sample size of N = 200, alpha = .05, one tailed, produces a power of .95.

E.13 ***Effect size between immune function and disease endpoint.*** Levy et al. (1991) provides relevant data from 90 women with Stage I or II breast cancer who were assessed at 15 months post diagnosis and followed for recurrence. This sample is similar to the one proposed here, and the timing of the assessment is particularly relevant as it would be similar to that proposed for the end of the 12 month intervention. They report r = .59 between NK cell activity and recurrence status. Using this figure as an estimate of the true effect size, the proposed N of 200 would yield power > .99.

E.2 Biostatistical Power Analyses

The cancer endpoint power analyses are of two types: comparison of differences in proportions at a given endpoint and median times (e.g. disease free interval) to an endpoint. An *evaluable patient* is defined as one who is treated according to the allocated trial arm, completes the assessments, and completes the years of follow up. This is in contrast to the number of *identified patients*, or the number of individuals who are approached for study participation. In the analyses below, we will assume a 25% rejection rate and a 25% drop out rate for the study. All of the power analyses we

have calculated indicate that a total sample size of N = 200 of evaluable patients is adequate for survival analyses, with many fewer subjects needed for analyses with recurrence as the endpoint. Since overall patient mortality is closely related to the time of intermediate events (e.g. recurrence), this may be more the important endpoint and the one we will explicitly test in the requested 4 year funding interval.

E.21 ***Proportions of recurrence at a given endpoint.*** We are using the metric of a *15-20% difference* in the proportion of patients remaining disease free, which is a standard metric in cancer clinical trials to indicate that one therapy results in a clinically important improvement over another. Our computation of required sample sizes for time to recurrence are based on the following data sources: 1) 5 year survival rates from the NCI's PDQ system for breast cancer (relevant pages can be provided upon request or obtained through the NCI's PDQ info service.); 2) recurrence rates; and, 3) local experience on the relative proportion of patients with Stage II and III breast cancer. First, the PDQ data state that 5 year survivals for stage II and III breast cancer are 66% and 41%, respectively. During a five year interval, the proportion of women developing recurrent disease is approximately equal to the proportion dying of disease plus 10%. At the Ohio State University, the ratio of stage II to stage III newly diagnosed cases is approximately 3:1. Also, the most recent data (1992) for Franklin County (the county which surrounds Columbus) for stage specific breast cancer diagnoses in the county also indicate a 3: 1 ratio. Using these figures, the overall 5 year survival for women with Stage II-III breast cancer at OSU is [(0.66)(0.75) + (0.41)(0.25)] = 60%, while the proportion of women demonstrating recurrence during the 5 years is approximately (1.00 - 0.60 + 0.10) = 50%.

We will test differences between the intervention and control groups with respect to proportions of patients showing recurrence of disease. If the true population difference is 50% for the control group and 30% for the intervention group, a total of 73 evaluable patients will be needed per treatment group (Total N of 146) by the end of the study (level of significance = 0.05, power = 0.80, one sided test). Again, assuming a 25% rejection rate and a 25% drop out rate, we will need to identify a total of 258 patients for the study (73 x 2 x 1.33 x 1.33 = 258) to determine the effect of treatment on recurrence. If the true population difference is 60% vs. 30%, we will need 33 evaluable patients per treatment group (Total N of 66) or, given assumptions stated above, a total of 117 (33 x 2 x 1.33 x 1.33 = 117) eligible patients to be approached about entering the study.

E.22 ***Median time to recurrence (Disease Free Interval, DFI).*** We will assume that treatment effects will be uniform for all prognostic subgroups/disease stages and that failure times (e.g. time of recurrence) will be exponentially distributed with uniform censuring. The evaluation of an effect due to the psychological intervention will be dependent upon the number of patients reaching the endpoints of interest and the proportion of patients in the prognostic subgroups used for stratification. We are using the metric of a *doubling of time to an endpoint*, which is a standard median time metric in cancer clinical trials to indicate that one therapy results in a clinically important improvement over another.

To detect a true treatment effect corresponding to a doubling of time to recurrence, we would require observing recurrence in 27 patients per treatment group (level of significance = 0.05, power = .80, one-sided test). If 50% of the patients demonstrate recurrence within the study interval, we will need 54 evaluable patients per treatment group. Assuming a 25% rejection rate and a 25% drop-out rate, we will need to identify a total of 192 patients for the study [(52 x 2 x 1.33 x 1.33) = 192] to determine the effect of treatment on time to recurrence.

E.3 Principal analyses: Statistical

E.31 ***Group differences/Intervention effects.*** Major hypotheses involve the expectation of significant group differences by time (Intervention vs. Control). Investigation of such effects will be accomplished primarily via the use of repeated-measures multivariate analysis

of covariance (MANCOVA). The primary design will be a group by time points design, with dependent variables being the psychological measures (stress, emotional adjustment, social adjustment, etc) and immune measures. Dependent variables will be grouped by content area so as to take into account their intercorrelations, as well as to reduce the number of separate significance tests that are conducted. Of particular interest will be the Group x Time interaction, indicating any differential change between groups due to the intervention. Analyses will also be conducted using the stratification variables (tumor size/nodal status, ER/PR status, menopausal status, presence of a spouse) as additional independent variables. We will examine the Group x Time x Status interaction effect for each of these stratification status indicators, so as to assess whether the intervention works differentially for different kinds of patients.

The analyses just described are stated in terms of measured variables. Implicit in this project is the notion that there exist latent variables (e.g., stress, emotional adjustment, social adjustment, immune functioning, etc.), each of which is measured with multiple indicators. The existence of these latent variables will be evaluated using confirmatory factor analysis. Assuming fundamental latent variables can be verified, group differences in means on latent variables will be evaluated via the analysis of structured means and multiple groups in confirmatory factor analysis models. This approach has the advantage of reducing the impact of error of measurement, which can strongly influence results of analysis of variance. In addition it greatly reduces problems associated with the analysis of multiple measured variables.

E.32 ***Relationships among variables--test of the model.*** To test the associations among variables specified in the biobehavioral model, bivariate relationships will first be evaluated using simple correlations and contingency tables. More complex relationships will be investigated using multiple regression methods. For example, hierarchical regression with sets of independent variables will be used in which immune outcomes are regressed on measures of stress and quality of life. Analyses will focus on the amount of variance explained in the dependent variables as well as the unique contribution of each of the independent variables in accounting for that variance, as measured by squared semi-partial correlations. These analyses will be conducted both within and across groups of subjects, as well as within and across time points.

Associations among variables will also be evaluated at the level of latent variables using structural equation modeling. We will develop and test models of relationships among such variables using the LISREL 8 computer program. For example, one model would be that stress and QoL are correlated exogenous latent variables that influence immune functioning, which in turn influence health. Each of these latent variables is represented by multiple measured variables, or indicators. This model as well as others (e.g. stress exerting independent effects--not mediated by immunity--on health outcomes) will be evaluated for goodness of fit to the observed data. These analyses will be conducted at each time point and will be extended to longitudinal form to evaluate the reliability and validity of the variable relationships.

E.33 ***Individual differences.*** We expect that individuals will vary with respect to their patterns of change over time on relevant variables, such as stress and immune function. We will examine individual differences in patterns of change over time using hierarchical linear models (HLM; Bryk and Raudenbush, 1993). For example, each individual will exhibit a unique pattern of change over time in stress. For subjects in the intervention group, we hope to see an improvement in this measure (i.e. a reduction in stress), followed by stabilization. Such a pattern can be represented by a mathematical model of change, where parameters in the model describe an initial level of stress, a linear trend, and a nonlinear (acceleration or stabilization) trend. Individual differences in these parameter estimates will be predicted from other variables, including background variables and stratification factors (tumor size/nodal status, ER/PR status, menopausal status, presence of spouse). Similar analyses will be conducted using HLM to assess individual differences in change with regard to immune function, disease progression, and other relevant dependent measures. Results should help explain individual differences in response to the

psychological intervention, as well as to account for individual differences in patterns of change for control subjects. This methodology has very important and useful aspects---it does not require that individuals be as the same disease stage upon entry into the study, nor that all individuals be measured at the same points in time, or that subjects have the same number of data points (Bryk & Raudenbush, 1993). We will use indicators of initial disease stage along with other more interesting psychological individual difference measures (i.e. extraversion, neuroticism, openness, and conscienciousness) to predict variation in patterns of change.

Finally, we also plan to investigate social support as a key individual difference variable, given its well-documented role as a predictor of mortality in epidemiological studies [House, Umberson, & Landis, 1988; there are parallel data linking marital status to stage and survival among cancer patients (Goodwin, Hunt, Key, & Samet, 1987)] as well as immunological studies (conflict interactions in Kiecolt-Glaser et al., in press). As has been done previously, we will explicitly explore social support factors in the prediction of immunity and health outcomes.

E.4 **Principal analyses: Biostatistical analyses of cancer endpoints.**

Cox regression (Cox 1972) analysis will be used to test hypotheses about the relationships between stress, immune responses, and intervention. This semi-parametric regression technique assumes that these factors act multiplicatively on a baseline hazard rate. Adjustments for initial conditions (e.g. hormonal status, number of nodes) will be made by either including an appropriate term in the model or by stratifying if the proportionality assumption is violated. The Cox model can incorporate time dependent covariates (e.g. serial measurements of immune and mental health status). Summary survival curves for all events will be computed by using the Kaplan-Meier estimator. Estimation and tests of hypothesis for the association between risk factors and illness will be made by using an Markov illness model (See Andersen et al. 1991). These techniques use a Cox model which makes adjustments to the risk set for delayed entry into the at risk cohort to prevent the problem of length bias sampling.

CONCLUSIONS

To summarize, we view stress, QoL, health behaviors, and compliance as the major factors in a conceptual model of adjustment to the cancer stressor. Also part of the model is the physiological system--the immune system--which may be one of the more important ones for moderating the effects of stress on disease processes. More specifically, we would look to NK cell function as providing an important "window" on this process. The literature confirms that QoL benefits accrue from psychological interventions. In contrast, health behaviors and compliance have rarely been an intervention target, although data suggest that such a broadened approach would be effective and provide added power in the examination of stress/immunity question.

The context of randomly assigning individuals to conditions that will result in differential psychological and behavioral outcomes (Andersen, 1992) provides one of the necessary conditions for an experimental test of the biobehavioral model. A "simple" experimental design--treatment vs. no treatment--would be the strategic next step, as such a design provides cause--effect data for the presence of an intervention producing enhanced psychological and behavioral outcomes, immune responses, and health effects. Once an effect is reliably demonstrated, it would then be relevant to study treatment component questions. Relevant literatures suggest that an intervention should emphasize relaxation, coping, social support, and disease-specific components (Andersen, 1992; Kiecolt-Glaser & Glaser, 1992). A randomized trial would need to not only produce immediate (acute) posttreatment changes, but also include elements to insure that change processes continue. Addition of a maintenance component, would be a novel addition to intervention research in cancer. Also, a maintenance component may be critical to achieve the longterm psychological /behavioral gains necessary to effect immune responses and/or disease progression. In sum, the biobehavioral model provides a testable, conceptualization for PNI research in breast cancer and

provides an opportunity to test for specific biologic or health consequences of psychological/behavioral interventions for breast cancer patients.

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Zielinsky, C.C., Tichatschek, E., Muller, C., Kalinowski, W., Sevelda, P., Czerwenka, K. (1989). Association of increased lytic effector cell function with high estrogen recoptor levels in tumor-bearing patients with breast cancer. *Cancer, 63,* 1985-1989.

Biographic Sketch

Name: Barbara L. Andersen **Position:** Principal Investigator

Education:

University of Illinois, Urbana-Champaign	B.S.	1973	Psychology
University of Illinois, Urbana-Champaign	M.A.	1978	Psychology
University of Illinois, Urbana-Champaign	Ph.D.	1980	Clinical Psychology
University of California, Los Angeles	Post doc	1980	Clinical Psychology

Employment/Experience

1991-present Professor, Dept. of Psychology and Dept. of Obstet. and Gynec., Ohio State University
Member, Arthur James Comprehensive Cancer Center, OSU.
1989-1991 Assoc. Professor, Dept. of Psychology and Dept. of Obstet. and Gynec., Ohio State University
1985-1989 Assoc. Professor, Dept. of Psychology and Dept. of Obstetrics and Gynecology, Univ. of Iowa
1986 Fall Visiting Fellow, Department of Psychology, Yale University
1980-1985 Assistant Professor, Department of Psychology, University of Iowa
1979-1980 UAF/Psychology Postdoctoral Fellow, Neuropsychiatric Institute, UCLA

Awards, Honors, and Special Recognition

Edmund James Scholar, University of Illinois, 1971-1973; B.S. with High Honors and High Distinction in Psychology, 1973
Psi Chi, 1972; Phi Kappa Phi, 1973; Sigma Xi, 1982
Burlington Northern Achievement Award for Excellence in Teaching, 1985
Fellow, Academy of Behavioral Medicine Research, 1987; Fellow, American Psychological Association, 1988
Gadeski Professor, Cross Cancer Inst. and the University of Alberta-Edmonton and UAB-Calgary, Canada, 1987
University of Iowa Research Scholar Award, 1988-1991

Editorial and Grant Review Responsibilities

Associate Editor: *Annals of Behavioral Medicine,* 1990-1993
Journal of Consulting and Clinical Psychology, 1991-present

Editorial Board: *J ournal of Consulting and Clinical Psychology,* 1986-1989
Journal of Social and Clinical Psychology, 1986-present
Journal of Psychosomatic Obstetrics and Gynaecology, 1987-present
Journal of Sex Research, 1989-1992
International Review of Health Psychology, 1990-present
Psychology of Women Quarterly, 1994-present

Grant Review and Recent Federal Government Service:

Member, Psychosocial I Panel, Breast Cancer Research Program, Department of the Army, Feb 1994.
Chair, Psychology Review Committee, U.S. Army Medical Research and Material Command, Breast Cancer Research Program, Nov. 1994
Member, Psychosocial and Behavioral Review Committee, American Cancer Society, 1995-present
Chair, Psychology Review Committee, Defense Women's Health Research Program, Department of the Army, November 1994
Invited participant, Women in Science and Technology Briefing, The White House, Mar 9, 1995
Chair, Psychosocial/Behavioral Panel; NIH Office of Women's Health Research, Breast Cancer Research, July, 1995.
Chair, Psychosocial I Panel, Breast Cancer Research Program, Department of the Army, Nov 1995.

Time Commitments

Research 50% (80% of this time is devoted to this project), Teaching 40%, Service 10%.

Current supervision:

Graduate students: Susan Aarestad, B.A., J. Cyranowski, M.A., Derek Espindle, B.A., Elizabeth Nielson-Gammon, B.S., J.D.

Research staff: Deanna Golden-Kreutz, Ph.D., Nicole Chaput, B.S., Angie Collier, B.A., Scott Cravens, Hilliary Houp, and assorted work study, undergraduate, and medical student assistants.

Representative publications prior to 1992 (Total N of 48):

Redd, W.H., Porterfield, A.L., & Andersen, B.L. (1979). *Behavior modification: Behavioral approaches to human problems*. New York: Random House.

Andersen, B.L. (1981). A comparison of systematic desensitization and directed masturbation in the treatment of primary orgasmic dysfunction in females. *Journal of Consulting and Clinical Psychology, 49,* 568-570.

Andersen, B.L. (1983). Primary orgasmic dysfunction: Diagnostic considerations and review of treatment. *Psychological Bulletin. 93,* 105-136.

Andersen, B.L., Karlsson, J.A., Anderson, B.A., & Tewfik, H.H. (1984). Anxiety and cancer treatment: Response to stressful radiotherapy. *Health Psychology, 3,* 535-551.

Andersen, B.L., & Tewfik, H.H. (1985). Psychological reactions to radiation therapy: A reconsideration of the adaptive aspects of anxiety. *Journal of Personality and Social Psychology, 48,* 1024-1032.

Andersen, B.L., & Jochimsen, P.R. (1985). Sexual functioning among breast cancer, gynecologic cancer, and healthy women. *Journal of Consulting and Clinical Psychology, 53,* 25-32.

Andersen, B.L. (Ed.). (1986). *Women with cancer: Psychological perspectives*. New York: Springer-Verlag.

Turnquist, D.C., Harvey, J.H., & Andersen, B.L. (1988). Attributions about life threatening illness. *British Journal of Clinical Psychology, 27,* 55-65.

Andersen, B.L., Anderson, B., & deProsse, C. (1989). Controlled prospective longitudinal study of women with cancer: I. Sexual functioning outcomes. *Journal of Consulting and Clinical Psychology, 57,* 683-691.

Andersen, B.L., Anderson, B., & deProsse, C. (1989). Controlled prospective longitudinal study of women with cancer: II. Psychological outcomes. *Journal of Consulting and Clinical Psychology, 57,* 692-697.

Andersen, B.L. (1989). Health psychology's contribution to addressing the cancer problem: Update on accomplishments. *Health Psychology, 8* , 683-703.

Redd, W.H., Silberfarb, P.M., Andersen, B.L., et al. (1991). Working group report: Physiologic and psychobehavioral research in oncology. *Cancer, 67,* 813-822.

Andersen, B.L. & LeGrand, J. (1991). Body image for women: Conceptualization, assessment, and a test of its importance to sexual dysfunction and medical illness. *The Journal of Sex Research, 28,* 457-477

Representative Publications from 1992-present (Total N of 37)

Andersen, B.L. (1992). Psychological interventions for cancer patients to enhance the quality of life. *Journal of Consulting and Clinical Psychology, 60,* 552-568.

Andersen, B.L. (1992). Breast cancer: Prevention and control. *Annals of Behavioral Medicine, 14,* 187-188.

Andersen, B.L., & Doyle-Mirzadeh, S. (1993). Breast cancer. In D.E. Stewart & N. L. Stotland (Eds.), *Psychological aspects of woman's health care: The interface between psychiatry and Obstetrics and Gynecology*. Amer. Psychiatric Press, Inc. (pg. 425-446).

Andersen, B.L. (1994). Yes, there are sexual problems problems. Now, what can we do about them? *Gynecologic Oncology, 52,* 10-13. (Invited commentary).

Andersen, B.L., Kiecolt-Glaser, J.K., & Glaser, R. (1994). A biobehavioral model of cancer stress and disease course. *American Psychologist, 49,* 389-404.

Andersen, B.L., & Cyranowski, J.C. (1994). Women's sexual self schema. *Journal of Personality and Social Psychology,* 1079-1100.

Andersen, B.L. (1994). Surviving cancer. *Cancer, 74,* 1484-1495.

Andersen, B.L., Cacioppo, J.T., & Roberts, D. (1995). Delay in seeking a cancer diagnosis: Delay stages and psychophysiologic comparison processes. *British Journal of Social Psychology, 34,* 33-52.

Andersen, B.L., & Golden-Kreutz, D. (in press). Biobehavioral views of cancer. In A. Baum (Eds.), *Handbook of health psychology*. Erlbaum.

Andersen, B.L. (in press). Cancer in women. In E.A. Blechman and K. Brownell (Eds.), *Behavioral medicine for women: A comprehensive handbook.* Guilford Publications

Andersen, B.L., & Cyranowski, J.C. (in press). Female sexuality: Behavior, responses, and individual differences. *Journal of Consulting and Clinical Psychology.*